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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/768,827	01/24/2001	Robert Schlegel	MRI-007A	2603

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EXAMINER	
SHEINBERG, MONIKA B	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/768,827	SCHLEGEL ET AL.	
	Examiner	Art Unit	
	Monika B Sheinberg	1634	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *2,7-9,22,27-43,45 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,10-21,23-26,44,46-49 and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-53* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Dtailed Action* .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 2, 7-9, 22, 27-43, 45 and 50) and SEQ ID NO: 10, in the response filed: 25 June 2003, is acknowledged.

Claims 2, 7-9, 22, 27-43, 45 and 50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the response filed: 25 June 2003. Please note however, that the sequence restriction was a restriction requirement and not a species election as per the mailed Restriction: 23 March 2003.

- Claims 1-53 are pending.
- Claims 2, 7-9, 22, 27-43, 45 and 50 are withdrawn.
- Claims 1, 3-6, 10-21, 23-26, 44, 46-49 and 51-53 are hereby examined with respect to SEQ ID NO: 10.

NOTE: Applicant is requested to point to the page number of each table that provides support for the method with respect to SEQ ID NO: 10 due to the numerous amount of information listed with respect to over 7500 sequences. It is difficult to find which information of clones, accession numbers and data are correlated to SEQ ID NO: 10 that may exist and that remains consistent; for example table 4-1 states sequence ID 10 is accession number AA885293 while table 3-1 states that it is accession number AB007870; clone numbers such as H51549 and H20747 are corresponding to a 'order 10' in two different tables. In addition, there are inconsistent labeling/titles: Table 1-1 goes by clone numbers, Table 2-1 has gene or order numbers, Table 3-1 says sequence #, Table 4-1 says sequence ID, and so forth. Page 108 states simply that they all correspond to "nucleotide sequence listed", but no information as shown above remains consistent.

Sequence Non-Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2).

However, this application fails to comply with the requirements of 37 CFR § 1.821 through 1.825 because page 34, line 8 contains a nucleic acid sequence without a sequence identifier and it is uncertain if it has been included within the Sequence Listing. The sequence presented in the specification must still be included in the Sequence Listing; and a sequence identifier (SEQ ID NO: X) must be used in the specification. A Sequence Listing and a computer readable format of it must be provided with a statement that the two are identical. Applicant is reminded that CD-ROM sequence listings are now accepted instead of a paper copy of the sequence listing for the specification. Applicant(s) are given the same response time regarding this failure to comply as that set forth to respond to this office action. A complete response to this office action includes compliance with this sequence rule compliance. Failure to comply may result in abandonment of this application.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, it is unclear as to where in the listed provisional applications upon which priority is claimed adequate support under 35 U.S.C. 112 has been provided for claims 1, 3-6, 10-21, 23-26, 44, 46-49 and 51-53, with respect to SEQ ID NO: 10 of this application. Priority date of the instant application is therefore considered to be January 24, 2001. Applicants are requested to provide page and line numbers for support of priority from the provisional applications listed as basis for priority. In addition, if the application from which priority is claimed, please indicate whether there is a computer readable format of the Sequence Listing.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

- ***Enablement***: Claims 1, 3-6, 10-21, 23-26, 44, 46-49 and 51-53, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPA 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are broadly drawn to methods of assessing whether a patient is afflicted with prostate cancer by comparing marker expression levels, and more specifically expression levels of SEQ ID NO: 10, between a patient's sample and a control non-prostate cancer sample; to methods of monitoring the progression of prostate cancer in a patient by comparing marker expression levels, and more specifically expression levels of SEQ ID NO: 10, between a patient's samples taken at sequential time points; and to methods of determining whether prostate cancer has metastasized in a patient by comparing marker expression levels, and more specifically expression levels of SEQ ID NO: 10, between a patient's sample and a normal or non-metastatic control sample.

The art does not establish a correlation between SEQ ID NO: 10 and prostate cancer.

The specification asserts that SEQ ID NO: 10 is a marker for prostate cancer that can be used in methods of "diagnosis, staging, prognosis, monitoring, and treatment of diseases associated with prostate cancer, or to indicate a predisposition to such for preventative medicine" which is an improvement over current methods in which protein markers associated to prostate cancer are found to be not able to distinguish between benign and malignant prostate tumors (p. 3, lines 1-13). In order to analyze the enablement of the methods to which the clams are drawn, the marker itself that the methods are based upon, has been examined first. The specification teaches the marker to be SEQ ID NO: 10, which was identified by subtractive library

hybridization techniques (page 98). The specification teaches that SEQ ID NO: 10 was identified from library cMhqaa. The specification teaches that the library-designated cMhqaa and cMhqsb was CDNA prepared from benign prostate hyperplasia and activated lymphocytes (page 99). The specification has provided many results in numerous tables demonstrating the overexpression of various markers, yet none can be referred to for evidence because it is uncertain as to what is a specific result of SEQ ID NO: 10 analysis.

The claims are broadly drawn to an association between SEQ ID NO: 10 and any sample in any population and prostate cancer at any stage of the disease. SEQ ID NO: 10 is correlated to different accession numbers that contain sequences much greater than that of the elected sequence itself. SEQ ID NO: 10 appears only to be a fragment of these thus it is confusing as to what applicant intends to be representative of the elected sequence; that which was submitted in the Sequence Listing or disclosed in the tables (which are themselves not clear). The specification does not teach whether the data generated in these tables came from results of experimentation with the full sequences that are disclosed in the GenBank entries, or from experimentation with the fragment that is disclosed in the sequence listing as SEQ ID NO: 10.

The teachings of the specification do not establish that one could actually detect expression of SEQ ID NO: 10 as an indicator of prostate cancer. The specification has performed a subtractive library hybridization technique in which the driver was prepared from benign prostate hyperpalsia and activated lymphocytes and wherein the tester was prepared from stage T3NO tumors. This difference detected by subtractive library hybridization technique does not establish that expression levels between benign prostate hyperplasia and tumors are significant in detecting prostate cancer. Rather the teachings of the specification asserts that "as a greater number of patient samples are assessed for expression of the markers of the invention and the outcomes of the individual patients from whom the samples were obtained are correlated, it will also be confirmed that altered expression of certain of the markers of the invention are strongly correlated with malignant cancers and that altered expression of the markers of the invention are strongly correlated with benign tumors" (page 23, lines 20-24). The tables presented in the specification which concurrently appear to display these results, have a multitude of results demonstrating altered expression yet none specific to SEQ ID NO: 10 (besides the inconsistency in correlated data). Thus it is uncertain if the specification has performed analysis studies to

determine whether SEQ ID NO: 10 has altered expression and whether the altered expression is strongly correlated with either malignant cancers of benign tumors. Therefore, the skilled artisan would be required to perform further research to confirm the use of SEQ ID NO: 10 expression as a marker for prostate cancer. The specification has not provided any indication of expression levels clearly specific to SEQ ID NO: 10 in either normal tissue, benign tumors, or malignant prostate cancer. Therefore, determining whether the expression level of SEQ ID NO: 10 would first require the skilled artisan to ascertain the range of expression levels of SEQ ID NO: 10 within various tissues prior to being able to establish whether SEQ ID NO: 10 expression is indicative of normal, benign or malignant prostate tissues. Upon determining whether there is expression within these tissues, the skilled artisan would be required to determine the ranges of the expression to establish thresholds which would be indicative of normal, benign or malignant tissue state. Furthermore, the specification has provided many results demonstrating the overexpression of various markers and none with underexpression; but the specification has provided no guidance as to whether SEQ ID NO: 10 itself is overexpressed in cancerous prostate tissue or whether SEQ ID NO: 10 is underexpressed in cancerous prostate tissue.

The tables provided potentially present validation assays of SEQ ID NO: 10's alter expression levels, however the examiner has been unsuccessful in correlating any consistent data specific to SEQ ID NO: 10. Evidence of expression levels have been provided for a plethora of different sequences however examiner has been unsuccessful in finding any link to the elected sequence in the tables or through GenBank that remains consistent. The GenBank entries pointed to are not limited prostate as indicated but to bone, brain, prostate, pooled samples etc. For example: Table 3-1 discloses accession number AB007870 to be representative of SEQ ID NO: 10, but review of the GenBank entry, the sequence was over 6000 base pairs greater that that of SEQ ID NO: 10 in the Sequence Listing and isolated from human brain (not noted whether male or female); Table 4-1 discloses accession number AA885293 to be representative of SEQ ID NO: 10, but in review of the database entry, the sequence was more than twice the Sequence Listing entry and was purified from pooled human samples (again no indication of male or female); Table 5-1 correlates accession number H09966 to 'order' 10, but review of the database entry indicated the sequence came from a female. Thus evidence of altered expression levels is inconclusive. It is unknown which clone, which accession number, which results are

representative of the data that is correlated to SEQ ID NO: 10. Without these correlations, the specification fails to provide an association with the instant method since the sequence data cannot be found; further, the specification fails to provide any statistical differences in expression of SEQ ID NO: 10 between normal, benign, and cancerous prostate tissue samples.

Applicant is requested to point to each table specifically to provide evidence for the experimental validation of altered expression levels specific to SEQ ID NO: 10 (please include page number along with applicable row and column information). Applicant is also requested to clarify whether or not the data is a result of the fragment SEQ ID NO: 10 provided in the Sequence Listing or the GenBank entries pointed to be representative of the elected sequence in different tables.

Upon results of a sequence analysis, SEQ ID NO: 10 demonstrated high alignments thus ability to hybridize under stringent conditions to multiple sequences from a plethora of tissues (adrenal gland, brain, lung, uterus, ovary and pooled samples; see attached sequence results); thus the specification is not enabled in how the instant marker sequence could be useful for methods of diagnosis, staging, prognosis, monitoring prostate cancer as stated by the specification.

The specification provides no working examples of methods of assessing whether a patient is afflicted with prostate cancer by comparing marker expression levels, and more specifically expression levels of SEQ ID NO: 10, between a patient's sample and a control non-prostate cancer sample; to methods of monitoring the progression of prostate cancer in a patient by comparing marker expression levels, and more specifically expression levels of SEQ ID NO: 10, between a patient's samples taken at sequential time points; and to methods of determining whether prostate cancer has metastasized in a patient by comparing marker expression levels, and more specifically expression levels of SEQ ID NO: 10, between a patient's sample and a normal or non-metastatic control sample. Further, the specification does not teach of any specific level of expression that can be predictably correlated with the severity of prostate cancer.

If the marker, SEQ ID NO: 10 is not enabled then the methods of using it are also not enabled. While working examples are not, per se, required, the specification must provide adequate guidance such that one of skill in the art could practice the invention without undue

experimentation. Given the lack of descriptive working examples in the specification, and the unpredictability of associating specific levels of marker expression with cancers, the specification, as filed is not enabling for the methods of using SEQ ID NO: 10 as claimed.

With respect to claim 1, drawn to a method of assessing whether a patient is afflicted with prostate cancer based upon the single marker, SEQ ID NO: 10, the specification does not provide evidence applicable to the altered expression levels of SEQ ID NO: 10 in prostate cell thus how is it useful for diagnosising, staging or monitoring prostate cancer. The specification does not teach the significant difference required (ie threshold value that must be surpassed) for indication that determining prostate cancer affliction. Such a teaching is necessary for the skilled artisan to be able to determine whether a predictable correlation exists between expression levels of SEQ ID NO: 10 and a patient afflicted with prostate cancer in order to ascertain a patient's affliction with prostate cancer. Since the specification does not provide any examples, which demonstrate assessment of a patient with or without prostate cancer, there is no guidance provided for method of assessing prostate cancer affliction. As stated previously, while working examples are not, per se, required, the specification must provide adequate guidance such that one of skill in the art could practice the invention without undue experimentation.

With respect to claim 17, drawn to a method of assessing whether a patient is afflicted with prostate cancer based upon a combination of markers including, SEQ ID NO: 10, the specification does not provide any specific association of SEQ ID NO: 10 in combination with levels of expression of any other sequences. The specification does not teach whether the observed levels of overexpression were in observed in combination together or separate. Such a teaching is required for the skilled artisan to practice the invention without undue experimentation because statistically significant association exists between the presence of each and every marker; for example, each marker being different would have a distinct expression level particular to only itself, yet genes work in together in a complex system therefore the expression of one marker in combination with another (at its own specific level of expression) may or may not result in symptoms of disease such as prostate cancer. In addition, the specification does not teach the level of significant association determinative of prostate cancer for each and every marker to be analyzed in the combination set, for each is different and distinct from each other; the predetermined threshold for one would not be same for another.

With respect to claim 21, drawn to a method of monitoring the progression of prostate cancer, the specification does not teach whether in the progression of cancer, is there an increase or decrease in expression levels that are associated; nor the threshold difference that must occur between sample expression levels to determine a change in patient status; nor the time points at which samples for monitoring should be taken. Such a teaching is necessary for the skilled artisan to be able to determine whether a patient's cancer has progressed or not, or has subsided. No examples have been provided to demonstrate the method of monitoring. Since the specification does not provide any examples as to predictable correlation between expression levels of SEQ ID NO: 10 and stages of prostate cancer, there is no guidance provided for method of monitoring. As stated previously, while working examples are not, per se, required, the specification must provide adequate guidance such that one of skill in the art could practice the invention without undue experimentation.

With respect to Claim 44, drawn to a method of determining whether prostate cancer has metastasized in a patient, the specification does not teach whether altered expression of SEQ ID NO: 10 is predictive of metastasis, nor the significant difference required (i.e. threshold value that must be surpassed) for indication that determining prostate cancer metastasized. The specification also does not indicate whether the sample is to be taken from multiple tissues to determine if the threshold expression level of SEQ ID NO: 10 has been met in each tissue (i.e. a lung tissue sample has the marker overexpressed therefore indicating metastasis to the lung); or a mere sample of any sort with altered expression of SEQ ID NO: 10 would render a conclusive answer of metastasis occurrence but not location (i.e. a blood sample that has the marker overexpressed at determined threshold value that indicates metastasis to the system/body as a whole without any particular location). A teaching of the required expression levels and the how the determination based on altered expression levels is made, is necessary for the skilled artisan to be able to determine whether expression levels of SEQ ID NO: 10 can be predictably associated with metastasis. No examples were provided. Since the specification does not provide any examples, which demonstrate determining whether prostate cancer has metastasized in a patient, there is no guidance provided for method of detecting metastasis. As stated previously, while working examples are not, per se, required, the specification must provide

adequate guidance such that one of skill in the art could practice the invention without undue experimentation.

With respect to Claim 49, drawn to a method of assessing the aggressiveness or indolence of prostate cancer, the specification does not provide what levels of expression are determinative of an aggressive or indolent prostate cancer; nor thresholds that must be met in order to classify the severity to be more aggressive than before. Such teachings are necessary for the skilled artisan to be able to determine the status of the cancer. No examples were provided. Since the specification does not provide any examples, which demonstrate assessing he aggressiveness or indolence of prostate cancer, there is no guidance provided for method of assessing the severity or lack of, of the cancer. As stated previously, while working examples are not, per se, required, the specification must provide adequate guidance such that one of skill in the art could practice the invention without undue experimentation.

Due to the lack of guidance from the specification as to any working examples or a statistically significant association between increased levels of expression of specifically SEQ ID NO: 10 and patients with prostate cancer or the levels of expression indicative of disease severity, the skilled artisan would be required to perform undue experimentation to practice the invention as claimed. The lack of guidance from either the specification or the art with regard to an association between SEQ ID NO: 10 and prostate cancer, such experimentation would require trial and error, the results of which are unpredictable. The claims merely provide the skilled artisan with an invitation to experiment and the specification provides no guidance as to a predictable correlation between the association of increased levels of expression of SEQ ID NO: 10 with prostate cancer. Therefore, given a) the quantity of experimentation necessary and that such experimentation requires trial and error, b) that the guidance from the specification only provides the skilled artisan with an invitation to experiment, and c) results of the trial and error analysis required by the skilled artisan are unpredictable, the skilled artisan would have to perform undue experimentation to practice the invention as claimed.

Specification Objections

The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other

form of browser-executable code in the specification in the following place: a) 20020168638; b) page 102, lines 21-25; and elsewhere in the specification. See MPEP § 608.01.

Conclusion

- Sequence non-compliance.
- Priority date: January 24, 2001.
- Claims 1, 3-6, 10-21, 23-26, 44, 46-49 and 51-53, are rejected under 35 U.S.C. 112, first paragraph – enablement.
- The disclosure is objected to.

No claim is allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Monika B. Sheinberg, whose telephone number is (703) 306-0511. The examiner can normally be reached on Monday-Friday from 9 A.M to 5 P.M. If attempts to reach the examiner by telephone are unsuccessful, the primary examiner in charge of the prosecution of this case, Jehanne Souaya, can be reached at 703-308-6565. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

September 8, 2003
Monika B. Sheinberg
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